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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

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| IN RE: | : | |
| Fosamax Products Liability Litigation | : | 1:06-md-1789 (JFK) |
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| *This Document Relates to All Actions* | : | |

**MEMORANDUM OF LAW IN SUPPORT OF DEFENDANT'S MOTION TO EXCLUDE EXPERT TESTIMONY ON *DAUBERT GROUNDS***

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## INTRODUCTION

Defendant Merck & Co., Inc. ("Merck"), by its attorneys, files this memorandum in support of its Motion to exclude Plaintiffs' experts under Federal Rules of Evidence 702 and 403 and *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 597-98 (1993).[1]

This is not a routine *Daubert* motion. The general causation opinions challenged by this Motion are not routine expert opinions, but instead rely upon theories that have been found unproven by mainstream science, as shown in numerous, published position papers issued by reputable scientific bodies. Although Plaintiffs' experts have pushed their fringe, outside the mainstream opinions in commercial books and conferences, their speculative opinions are not suitable for sworn testimony before jurors in a court of law.

Similarly, the three witnesses designated by Plaintiffs as experts to testify on issues other than general causation also do not present routine expert testimony. Instead, they proffer "bad company" opinion testimony, which the federal courts repeatedly have excluded. Plaintiffs' experts Suzanne Parisian and Curt Furberg try once again to submit improper opinions that other courts have rejected or have stricken from evidence. Just within the past year, Parisian has been excluded from testifying in one MDL proceeding and had her testimony stricken (along with the jury verdict based upon it) in another MDL proceeding. Furberg was excluded from testifying by this very Court when he proffered in the *Rezulin* MDL proceedings the same type of testimony that he now proffers here. Plaintiffs' other expert, Gordon Guyatt, presents a number of speculative, subjective opinions, none of which are grounded in fact, based on any knowledge he possesses, or relevant to Merck or to any specific Plaintiff.

[1] This brief is filed pursuant to Paragraph 2.1 of Case Management Order No. 15, which governs the filing of *Daubert* Motions. Accordingly, this motion addresses the admissibility of the Plaintiffs' designated expert testimony under the standards articulated in *Daubert*, which applied Rules 702 and 403.

This motion is organized to address the failings of Plaintiffs' proffered expert testimony in a coordinated fashion. Section I, *infra,* sets forth the legal standard that each of Plaintiffs' experts must meet before his or her testimony may be admitted.

Section II, *infra*, addresses Plaintiffs' general causation experts. Plaintiffs have proffered Robert E. Marx, John W. Hellstein, Mahyar Etminan, and Alastair N. Goss as experts on general causation issues. It is the scientific consensus, established in position papers issued by numerous reputable scientific bodies, that no causal relationship has been proven between oral bisphosphonates and ONJ. This consensus exists for two basic reasons: (1) There are no controlled studies proving that oral bisphosphonates are associated with an increased risk of ONJ, and (2) there is no known or tested biological mechanism to explain why Fosamax would cause ONJ. To contradict this scientific consensus, Plaintiffs' experts cite case reports and speculative theories about biological mechanisms that the scientific community recognizes as unproven. Section II details why their testimony based on speculative theories and methodological errors is not admissible.

Sections III through V, *infra*, address Plaintiffs' second group of experts, Suzanne Parisian, Curt Furberg, and Gordon Guyatt, whose opinions are dressed up in various science-like guises, but in essence seek to introduce opinion testimony regarding "company conduct" that has repeatedly been found not to be the proper subject of expert opinion. Furberg and Parisian present the same narrative descriptions of regulatory history, speculations as to Merck's motives, unsupported contentions about the promotion of Fosamax, and unsupported assertions as to the governing standard of care for which other MDL courts have excluded their testimony or stricken jury verdicts based on it. *See In re Prempro Prods. Liab. Litig.*, 554 F. Supp. 2d 871

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Merck reserves the right to challenge portions of the testimony proffered by these experts on other grounds at the appropriate time, whether *in limine* or during trial.

(E.D. Ark. 2008) (striking jury verdict based on Parisian's testimony); *In re Human Tissue Prods. Liab. Litig.*, 582 F. Supp. 2d 644 (D.N.J. 2008) (excluding Parisian's testimony); *In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531 (S.D.N.Y. 2004) (hereinafter *"Rezulin I"*) (excluding Furberg's testimony). Guyatt presents views as to the promotion of Fosamax based on an opinion piece that he wrote in conjunction with others, but without any underlying facts that he can cite to support those opinions or any effort to tie those opinion to the issues in these cases.

Finally, Section VI, *infra,* sets forth additional reasons for excluding portions of the proffered expert testimony under *Daubert.*

## I. Plaintiffs' Expert Testimony Is Not Admissible Unless Plaintiffs Prove That It Is Based On Scientific Or Technical Knowledge The Experts Are Qualified To Present, Is Reliable, And Will Assist The Jury.

As Seventh Circuit Judge Richard Posner has written, "[l]aw lags science; it does not lead it," and the courtroom "is not the place for scientific guesswork, even of the inspired sort." *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996). A party who proffers an expert witness bears the burden of proving that the proposed testimony is admissible. *See* Fed. R. Evid. 104(a). Because expert testimony has the potential to "be both powerful and quite misleading," the Court must perform a critical "gatekeeper" role, by excluding purported expert testimony that is not based upon sound methodology and closely tied to the issues in the case. *See Daubert,* 509 U.S. at 595-98; *Kumho Tire Co., Ltd. v. Carmichael,* 526 U.S. 137, 147 (1999) (extending *Daubert* to technical and other specialized expert testimony). The Court must "make certain that an expert . . . employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co.*, 526 U.S. at 152; *see also In re Bextra & Celebrex Mktg., Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1171 (N.D. Cal. 2007) (*"In re Bextra III"*) (quoting *Kumho Tire*, 526 U.S. at 152).

The Court's gatekeeping rule is particularly important in complex litigation in which multiple plaintiffs seek to have a lay jury decide complicated and novel scientific claims, such as Plaintiffs' general causation opinions in this case, which have been thoroughly addressed by the relevant medical and scientific communities and found to be unproven. As the Court in the Human Tissue Products Multidistrict Proceedings, MDL No. 1763, recently observed, "[w]here there is little direct evidence proving an expert's conclusions or in a developing area of medicine and science, courts face particular challenges in determining whether the expert testimony is sufficiently reliable based upon the scientific and medical information presented to the court," and Plaintiffs' experts must "demonstrate 'good grounds' for all aspects of their proposed testimony, including 'the methodology, the facts underlying the expert's opinion, and the link between the facts and the conclusion.'" *In re Human Tissue Prods. Liab. Litig.*, 582 F. Supp. 2d at 657 (citation omitted).

To meet these goals, expert testimony is not admissible under Federal Rule of Evidence 702 unless it meets each of three requirements. *See* Fed. R. Evid. 702. First, the proposed testimony must be based on specialized knowledge that a witness is qualified to present. This requirement "guards against the admission of subjective or speculative opinions." *Rezulin I*, 309 F. Supp. 2d at 541 (citing *Daubert*, 509 U.S. at 590); *see also Smith v. Wyeth-Ayerst Labs. Co.*, 278 F. Supp. 2d 684, 691 (W.D.N.C. 2003) ("Speculation is not a reliable basis for expert opinion.") (citing *Daubert*, 509 U.S. at 590). It also ensures that the expert "will not testify about 'lay matters which a jury is capable of understanding and deciding without the expert's help.'" *Rezulin I,* 309 F. Supp. 2d at 541 (quoting *Andrews v. Metro North Commuter R.R. Co.*, 882 F.2d 705, 708 (2d Cir. 1989)).

Second, such testimony is not admissible unless the court determines that it is reliable. *See Rezulin I*, 309 F. Supp. 2d at 539 (citing *Daubert*, 509 U.S. at 592-93), 540 (noting that courts should not admit expert opinion evidence "which is connected to existing data only by the *ipse dixit* of the expert"); Fed. R. Evid. 702 (providing that the testimony must be based upon sufficient facts or data and the product of reliable principles and methods). In *Daubert*, the Supreme Court outlined four, non-exclusive factors that each trial court should consider when making this reliability determination: (1) whether the expert's theory "can be (and has been) tested"; (2) whether the theory "has been subjected to peer review and publication"; (3) the "known or potential rate of error"; and (4) "general acceptance" of the theory. 509 U.S. at 593-94.

Third, expert testimony is not admissible unless it assists the trier of fact. This means that the testimony must *both* be relevant to the specific issues in the case, *In re Bextra III*, 524 F. Supp. 2d at 1171 (quoting *Daubert v. Merrell Dow Pharmaceuticals*, 43 F.3d 1311, 1315 (9th Cir. 1995)), and it must not invade the province of either the Court or the jury, *United States v. Bilzerian,* 926 F.2d 1285, 1294 (2d Cir. 1991) (stating that expert testimony must be "carefully circumscribed").

Each step in an expert's opinion must independently meet these criteria for admissibility, and an opinion based even a single, unsupported link in its chain of reasoning should be excluded. *See In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 426 (S.D.N.Y. 2005) (excluding opinions where "[t]he plaintiffs have no evidence for the final link in their causal chain, and they extrapolate from the earlier links in ways the Court finds unreliable") (hereinafter "*Rezulin II*"); *Amorgianos v. Nat'l RR Passenger Corp.*, 137 F. Supp. 2d 147, 174-75 (E.D.N.Y. 2001), *aff'd*, 303 F.3d 256 (2d Cir. 2002) (finding proposed expert opinion inadmissible where it

contained a speculative step that assumed the rate of release of xylene from paint). As the Court noted in *Rezulin II*, "[a] crucial consideration in evaluating the admissibility of expert testimony is whether the conclusions flow reliably from the premises." 369 F. Supp. 2d at 426. As will be discussed with respect to each group of experts in Sections II through V, *infra*, Plaintiffs' experts fail to meet these requirements.

## II. Merck's Motion To Exclude General Causation Witnesses Marx, Hellstein, Etminan, And Goss.

### A. Introduction Regarding General Causation Witnesses.

The scientific consensus, as expressed in numerous reports by responsible professional and scientific organizations, is that it has not been proven that oral bisphosphonates cause ONJ. This consensus is based on the facts that no randomized, controlled trials or other controlled studies support an association between ONJ and oral bisphosphonates, no animal or in vitro studies show that such oral bisphosphonates cause ONJ, and there is no known mechanism by which oral bisphosphonates could cause ONJ. Despite this consensus, Plaintiffs proffer Robert E. Marx, John W. Hellstein, Mahyar Etminan, and Alastair N. Goss to provide opinion testimony on general causation.

The Court does not need to don a lab coat in order to determine that the methodology employed by these experts is impermissibly speculative and unreliable.[2] Plaintiffs' experts base

[2] In *Adesina v. Aladan Corp.*, 438 F. Supp. 2d 329 (S.D.N.Y. 2006), the Court stated that "[t]he flexible *Daubert* test does not require the judge to step into a white lab coat and perform a rigorous scientific analysis of the proposed expert testimony, but rather 'gives the district court the discretion needed to ensure that the courtroom door remains closed to junk science while admitting reliable expert testimony that will assist the trier of fact.'" *Id.* at 342 (quoting *Amorgianos v. Nat'l RR Passenger Corp.*, 303 F.3d 256, 267 (2d Cir. 2002)). Unlike this case, *Adesina* did not involve novel claims of causation, but instead centered on whether a doctor would be permitted to testify about a test she used in the course of treating a patient. *Id.* at 340. By contrast, the Plaintiffs' novel claims of general causation here require the Court to conduct the rigorous "preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid" described by the Supreme Court in *Daubert*, 509 U.S. at 592-93.

their opinions on case reports and hypotheses as to possible mechanisms that have not been proven, and seek to bolster this weak evidence with unsound prevalence studies and inapplicable animal data. Their arguments here are not unlike those made by the plaintiffs in *Hollander v. Sandoz Pharms. Corp.*, 95 F. Supp. 2d 1230 (W.D. Okla. 2000), *aff'd in relevant part*, 289 F.3d 1193 (10th Cir. 2002), in which the court excluded proposed expert testimony on general causation, after finding that the cumulative problems with the plaintiffs' evidence rendered their entire chain of reasoning unreliable. As the *Hollander* court noted:

> [D]ue to the absence of supportive epidemiological evidence, the differences between bromocriptine [the substance at issue] and the other ergot alkaloids, the dissimilarity of the animal studies, and the unreliability of the case reports, the data and methods relied on by the plaintiffs' experts do not furnish a scientifically valid basis for their conclusion that Parlodel causes strokes.

*Id.* at 1238-39. The same reasoning applies here, and the general causation opinions of Hellstein, Marx, Goss, and Etminan should be excluded in their entirety. In addition, as will be discussed below, many of the individual steps in these opinions lack basis or are outside of the expertise of Plaintiffs' experts, and are independently subject to exclusion.

### B. Background Regarding General Causation Issues.

#### 1. Fosamax And Its Mechanism Of Action As A Drug For Treatment And Prevention Of Osteoporosis.

The FDA approved Fosamax (alendronate) in 1995 as a medicine administered orally for the treatment of osteoporosis in post-menopausal women and Paget's disease of bone. In 1997, the FDA approved Fosamax for the prevention of osteoporosis. The intravenous ("IV") bisphosphonate Aredia was approved in 1991. Report of John P. Bilezikian, M.D. ¶ 16 ("Bilezikian Report") (Ex. 21).[3] IV bisphosphonates, including Aredia and Zometa, are

[3] References throughout this brief to "Ex. __" refer to the appropriately numbered exhibit attached to the Declaration of William J. Beausoleil filed by Merck concurrently with and in support of this Motion and Memorandum.

administered at a much higher dose than oral bisphosphonates, and Zometa in particular is a much more potent medication than Fosamax. Report of David W. Dempster, Ph.D. ("Dempster Report") at pp. 12-14 (Ex. 22). IV bisphosphonates are generally used in cancer patients to treat metastases and hypercalcemia of malignancy. *Id.* at 13.[4]

Osteoporosis causes bones to become more porous, making them weaker and more brittle, leading to low bone mass and an increased risk of fracture. Osteoporosis is the most prevalent bone disease in the United States, afflicting more than 10 million Americans over age 50, 80% of whom are women. Carmona, Richard H. et al., BONE HEALTH AND OSTEOPOROSIS: A REPORT OF THE SURGEON GENERAL, at 68 (U.S. Dept of Health and Human Servs., October 14, 2004) ("Surgeon General Report") (Ex. 28). Thirty-four million more Americans have low bone mass ("osteopenia") and are at risk of developing osteoporosis and bone fracture. *Id.* Four of every ten Caucasian women over age 50 will have an osteoporosis-related fracture in their remaining lifetime. *Id.* "The overall mortality from hip fracture alone is estimated to be 30 percent" and "only 40 percent of those who sustain a hip fracture are capable of returning to their prefracture level of independence." Schorge, *et al.*, *Chapter 21: Menopausal Transition*, Williams' Gynecology at 477 (1st ed. 2008) (Ex. 29).[5] Marx agrees that osteoporosis is a significant disease that creates a serious risk of morbidity and can cause life-threatening fractures. Deposition of Robert E. Marx of 06/01/07 at 184-86, 189 ("Marx Class Certification Dep.") (Ex. 1).

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[4] Aredia and Zometa are manufactured by Novartis Pharmaceuticals Corporation. In addition to Fosamax, the FDA has approved two other oral bisphosphonates, Actonel (manufactured by Procter & Gamble Pharmaceuticals and Sanofi-Aventis US) and Boniva (manufactured by Roche Laboratories, Inc.) for purposes of treating osteoporosis and/or Paget's disease. Bilezikian Report ¶ 20.

[5] Bone fractures are severe medical events. In one study, 20% of senior citizens died within a year of a hip fracture, and the Surgeon General reports that hip fractures account for 300,000 hospitalizations per year, with nearly 20% of elderly hip fracture patients ending up in nursing homes. Surgeon General Report at 91 (Ex. 28).

Osteoporosis results from an imbalance in the bone remodeling process. Bilezikian Report ¶ 10; Report of Elizabeth Holt, M.D., Ph.D. ("Holt Report") at 7-8 (Ex. 23). Throughout a person's life, his or her bones undergo a continuous process of remodeling, where mature bone is replaced by younger, more resilient bone. Bilezikian Report ¶ 10; Dempster Report at 6-7. Two of the components of bone remodeling are bone resorption (bone breakdown) by cells called osteoclasts and bone formation (the creation of new bone) by cells called osteoblasts. Bilezikian Report ¶ 10. The living bone itself, however, is comprised of a third kind of cells, called osteocytes. *Id.* When a woman ages, the rapid reduction of estrogen levels associated with menopause may stimulate the loss of bone by over-activating osteoclasts and the process of resorption. *Id.* ¶ 12. As a result, the remodeling process becomes unbalanced—the over-activated osteoclasts remove more bone than would otherwise be the case, and the body begins losing bone. *Id.* ¶ 12. If bone mass continues to decline, a person may become osteoporotic. *Id.* ¶¶ 9-15.

Fosamax reduces osteoclastic activity, thereby returning bone turnover to within the pre-menopausal range. Dempster Report at 10; Holt Report at 23 (noting "bone turnover markers in Fosamax-treated post-menopausal women are essentially identical to the bone turnover markers of healthy untreated premenopausal women"). Fosamax does not stop bone remodeling, and studies have shown continued bone turnover in women who have used Fosamax for up to 10 years. Holt Report at 22. Fosamax can increase or maintain bone mass, strengthen bones, and reduce the incidence of fracture, including severe fractures of the hip and spine. *Id.* at 35 ("That Fosamax treatment can reduce fracture risk by as much as 50% is evidence that it is a crucial part of our therapeutic armamentarium.").

### 2. ONJ Is A Rare, Non-Fatal Condition That Occurs In Conjunction With Many Potential Predisposing Factors.

ONJ is a very rare condition with no universally accepted definition and many symptoms that overlap with other medical conditions. ONJ generally refers to an area of exposed necrotic bone in the jaw that fails to heal after 6 to 8 weeks, and where the patient has not received craniofacial radiation. Report of Jeri W. Nieves, Ph.D. ("Nieves Report") at 10 (Ex. 24). ONJ occurs in the absence of any bisphosphonate, as shown by a significant body of literature, and as Plaintiffs' expert Dr. Hellstein admits. Deposition of John W. Hellstein of 3/25/09 ("Hellstein Dep.") at 86-87, 90, 130, 136-38, 142, 152 (Ex. 6); Report of Robert S. Glickman, M.D. ¶ 9 (Ex. 69). As recognized by Hellstein, "ONJ has been reported to result from radiation therapy of the head and neck, chronic corticosteroids therapy, herpes zoster virus infection in immunocompromised patients, uncontrolled infections and major trauma." Report of John W. Hellstein ("Hellstein Report") at 8 (Ex. 7). For example, one recent article detailed a case of ONJ, as adjudicated by dental professionals blinded to the patient's treatment, that was found in a patient taking the *placebo* in a randomized clinical trial testing the efficacy of zoledronic acid. Grbic, *et al.*, *Incidence Of Osteonecrosis Of The Jaw In Women With Postmenopausal Osteoporosis In The Health Outcomes And Reduced Incidence With Zoledronic Acid Once Yearly Pivotal Fracture Trial*, 139 J. AM. DENTAL ASS'N 32, 35-36 (Jan. 2008) (Ex. 30).[6]

[6]There are numerous other published, peer reviewed articles to the same effect. *See, e.g.*, Estillo, *et al.*, *Osteonecrosis Of The Jaw Related To Bevacizumab*, 26 J. CLIN. ONCOLOGY 4037 (2008) (two cases of exposed bone in the jaws of patients who did not take bisphosphonates and did not have radiation therapy to the head or neck) (Ex. 31); Greuter, *et al.*, *Bevacizumab-Associated Osteonecrosis Of The Jaw*, 19 ANNALS OF ONCOLOGY 2091 (December 2008) (case report of ONJ in patient who did not take bisphosphonates and did not have radiation therapy) (Ex. 32); Siwamogstham, *et al.*, *Herpes Zoster In HIV Infection With Osteonecrosis Of The Jaw And Tooth Exfoliation*, 12 ORAL DISEASES 500 (2006) (reporting on three cases of ONJ in HIV patients with herpes zoster and noting 20 previous cases of ONJ in the medical literature in patients with herpes zoster in the absence of HIV) (Ex. 33); Pires, *et al.*, *Oral Avascular Bone Necrosis Associated With Chemotherapy And Bisphosphonate Therapy*, 11 ORAL DISEASES 365 (2005) (reporting on two patients with ONJ who did not take bisphosphonates) (Ex. 34);

There are many potential risk factors for ONJ. The Task Force Report on ONJ for the American Society for Bone and Mineral Research ("ASBMR Task Force Report"), notes that ONJ may be associated with trauma, osteomyelitis, herpes zoster, benign sequestration of the lingual plate, and HIV-associated ulcerative periodontitis. Khosla, *et al.*, *Bisphosphonate-Associated Osteonecrosis Of The Jaw: Report Of A Task Force Of The American Society For Bone And Mineral Research*, 22 J. BONE & MINERAL RES. 1479, 1481 (2007) (Ex. 40). Plaintiffs' own experts concede that such risk factors exist for ONJ or exposed bone in the jaw, including osteomyelitis, denture sores, and cancer.[7]

Mouth infections of many varieties can lead to exposed bone in the jaw and hence to ONJ. Osteomyelitis, in particular, "is a diverse group of disorders that have in common an infection of the bone," and that can lead to "the death of the cells within the bone due to the infection." Holt Report at 26-27. As Hellstein admits, osteomyelitis may itself be caused by many different mouth infections, and osteomyelitis can then lead to osteonecrosis of the jaw. *See* Hellstein Dep. at 130, 133-34, 141-46. In addition, a number of significant contributing

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Erdogan, *et al.*, *Bony Palatal Necrosis In A Diabetic Patient Secondary To Palatal Rotational Flap*, 19 J. DIABETES & COMPLICATIONS 364 (2005) (reporting on patient with exposed, necrotic bone in the mouth; no mention of bisphosphonates or radiation therapy) (Ex. 35); Lenz, *et al.*, *Does Avascular Necrosis Of The Jaws In Cancer Patients Only Occur Following Treatment With Bisphosphonates?*, 33 JOURNAL OF CRANIO-MAXILLOFACIAL SURGERY 395 (2005) (case of ONJ in patient who did not take bisphosphonates and did not have radiation therapy to the head or neck) (Ex. 36); Peters, *et al.*, *Lingual Mandibular Sequestration And Ulceration*, 75 ORAL SURG. ORAL MED. ORAL PATHOL. 739 (1993) (case series of 11 patients who had not taken bisphosphonates and who experienced sequestering bone lesions that lasted from one week to three months) (Ex. 37); Schwartz, *et al.*, *Osteonecrosis Of The Jaws: A Complication Of Cancer Chemotherapy*, 4 HEAD & NECK SURGERY 251 (1982) (reporting on ONJ in two patients who had not taken bisphosphonates) (Ex. 38); Cooper, *Tooth Exfoliation And Osteonecrosis Of The Jaw Following Herpes Zoster*, 143 BRITISH DENTAL J. 297 (1977) (Ex. 39).

[7] Marx concedes that exposed bone in the mouth can be caused by osteomyelitis, trauma, herpes zoster, osteoradionecrosis, alveolar osteitis, denture sores, cancer, infections, and lingual mandibular sequestration and ulceration. (Deposition of Robert E. Marx in *Aredia & Zometa Prods. Liab. Litig.*, MDL No. 1760 ("Marx Aredia Dep."), at 44, 159, 611-12, 618, 630, 811-12 (Ex. 2); Deposition of Robert E. Marx of 8/04/08, ("Marx 8/04/08 Dep.") at 254 (Ex. 3); Deposition of Robert E. Marx of 3/27/09 ("Marx 3/27/09 Dep."), at 318 (Ex. 4). Hellstein similarly admits that many conditions can lead to ONJ or exposed jaw bone. Hellstein Dep. at 86-87, 137-38.

factors may affect healing of exposed bone in the jaw, when it occurs, that have nothing to do with bisphosphonates. Dr. Hellstein, for example, has testified that smoking causes delayed wound healing, that it increases the risk of exposed bone such as aleveloar osteitis ("dry socket"), that it increases the risk for infection, and that such infections themselves lead to ONJ. *Id.* at 133-34; *see also id.* at 126 (testifying that smoking increases the risk of osteonecrosis of the jaw).

No reports were published in the medical literature drawing any connection between any form of bisphosphonate and ONJ until September 2003, when Dr. Marx wrote a letter to the editor of the Journal of Oral and Maxillofacial Surgery identifying case reports of ONJ in patients on IV bisphosphonate therapy only. The first scientific article providing a case series of ONJ in *oral* bisphosphonate patients was published in the Spring 2004, almost nine years after Fosamax was approved for sale. Bilezekian Report ¶ 33.

### 3. The Scientific Consensus That There Is No Proven Causal Relationship Between Oral Bisphosphonates And ONJ Is Based On The Lack Of Controlled Studies Proving An Association And The Lack Of A Known Mechanism.

#### a. The Consensus Of The Scientific Community Is That Causation Remains Unproven.

Because of the lack of scientific evidence showing that oral bisphosphonates cause ONJ, the medical and dental communities have repeatedly rejected the conclusions of Plaintiffs' experts, and repeatedly affirmed that it has not been proven that oral bisphosphonates such as Fosamax cause ONJ. The American Dental Association ("ADA"), the American Association of Oral and Maxillofacial Surgeons ("AAOMS"), the Canadian Association of Oral and Maxillofacial Surgeons, the American Society for Bone and Mineral Research ("ASMBR"), and the European Society on Clinical and Economic Aspects of Osteoporosis have all concluded that a cause-and-effect relationship between oral bisphosphonates and ONJ has not been established.

*See* American Dental Association Council on Scientific Affairs, *Dental Management Of Patients Receiving Oral Bisphosphonate Therapy: Expert Panel Recommendations*, 137 J. AM. DENT. ASS'N 1144, 1145 (2006) ("To date, a true cause-and effect relationship between osteonecrosis of the jaw and bisphosphonate use has not been established.") (Ex. 41); AMERICAN ASSOCIATION OF ORAL AND MAXILLOFACIAL SURGEONS POSITION PAPER ON BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAW – 2009 UPDATE ("AAOMS 2009 Position Paper") ("the current level of evidence does not fully support a cause-and-effect relationship between bisphosphonate exposure and necrosis of the jaw") (Ex. 42); Kahn, *et al.*, *Canadian Consensus Practice Guidelines For Bisphosphonate Associated Osteonecrosis Of The Jaw*, 35 J. RHEUMATOLOGY 1391, 1395 (2008) ("the relationship between bisphosphonate use and ONJ in the patient with osteoporosis remains unproven") (Ex. 43); Khosla, *et al.*, *Bisphosphonate-Associated Osteonecrosis Of The Jaw: Report Of A Task Force Of The American Society For Bone And Mineral Research*, 22 J. BONE & MINERAL RES. 1479, 1481 (2007) (stating that "bisphosphonates have not proven to be causal") (Ex. 40); Rizzoli, *et al.*, *Osteonecrosis Of The Jaw And Bisphosphonate Treatment For Osteoporosis*, 42 BONE 841, 841 (2008) (reporting finding by European Society on Clinical and Economic Aspects of Osteoporosis that "No causative relationship has been unequivocally demonstrated between ONJ and bisphosphonate therapy.") (Ex. 44).

**b. There Are No Controlled Studies That Demonstrate An Association Between ONJ And Oral Bisphosphonates.**

A preliminary step in proving causation is to show that there is an "association" between a drug and an alleged condition. *See* Federal Judicial Center, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 348 (2d ed. 2000) (Ex. 45). An association exists when persons exposed to an agent experience the adverse event more frequently than persons not exposed to the agent, and

is most often quantified numerically as a relative risk or odds ratio. *Id.* However, "an association is not equivalent to causation." *Id.* at 336; *see also Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1315 n.16 (11th Cir. 1999) ("[S]howing association is far removed from proving causation."). Once an association is established, epidemiologists still must perform additional analyses to determine "whether the association reflects a true cause-effect relationship." REFERENCE MANUAL ON SCIENTIFIC EVIDENCE at 374. Plaintiffs' own experts admit that an "association" does not equate to "causation." Hellstein Dep. at 108; *see also* Deposition of Robert E. Marx in *Aredia & Zometa Prods. Liab. Litig.,* MDL No. 1760 ("Marx Aredia Dep."), at 1071-72 (Ex. 2).

Proof of an association between a drug exposure and a health condition requires study of both exposed and non-exposed populations. A randomized, placebo-controlled clinical trial is the recognized "gold standard" for determining whether a drug and a health outcome are associated. *See, e.g.*, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE at 338; *Rezulin II*, 369 F. Supp. 2d at 406.[8] Plaintiffs' experts concede that randomized, controlled trials are the best and most reliable experimental design for proving an association. *See* Deposition of Mahyar Etminan of 03/17/09 ("Etminan Dep.") at 112 (testifying that randomized controlled trials are "the gold standard" for "determining whether an adverse event is related to drug use") (Ex. 8); *see also* Etminan, *Evidence-Based Pharmacotherapy: Review of Basic Concepts and Applications in Clinical Practice*, 32 ANNALS OF PHARMACOTHERAPY 1193-1200 (Nov. 1998), at 1194 (Ex. 46) ("RCTs are the best experimental design to evaluate an outcome of interest.").

[8] In a randomized, controlled trial, the study subjects are randomly assigned to two groups: one group is exposed to the agent at issue, the other is given a placebo or a comparator agent. REFERENCE MANUAL ON SCIENTIFIC EVIDENCE at 338. After a period of time, the trial participants in both groups are evaluated for efficacy and adverse events. *Id.* Use of this study design "is the best way to ensure that any observed difference between the two groups in outcome is likely to be the result of exposure to the drug." *Id.*

There is *no* evidence from randomized clinical trials that Fosamax is associated with an increased risk for ONJ. The available data from randomized, controlled trials, in fact, fails to support any such hypothesis. Clinical trials of oral bisphosphonates for the treatment of osteoporosis have included over 60,000 patient years of study, including up to 10 years of follow-up in some patients, and there were no reports of ONJ. Bilezikian, *Osteonecrosis of the Jaw – Do Bisphosphonates Pose a Risk?*, 355 NEW ENG. J. MED. 2278-2281 (Nov. 30, 2006), at 2279 (Ex. 47). Plaintiffs can cite to no clinical trial evidence to support their claims.[9]

In the absence of a randomized controlled trial, controlled epidemiological studies provide a less certain means of establishing an association. *See Rezulin II*, 369 F. Supp. 2d at 406; *see also In re Joint Eastern & Southern Dist. Asbestos Litig.*, 52 F.3d 1124, 1128-29 (2nd Cir. 1995).[10] As Hellstein admits, Plaintiffs cannot cite any controlled study, of any design, in which exposed patients were compared to comparable unexposed patients and that demonstrated that Fosamax increased the risk for ONJ. Hellstein Dep. at 82, 90 (testifying that he was not "aware of any study that has applied the scientific method using both a case group and a control group to demonstrate that Fosamax increases the risk for osteonecrosis of the jaw"). Etminan, Plaintiffs' designated epidemiologist, concedes that there is an "absence" of epidemiological studies on whether bisphosphonates cause ONJ, and that he cannot calculate "any measure of association" between bisphosphonates and ONJ because the frequency of ONJ in non-bisphosphonate patients is unknown. Etminan Dep. at 101, 290.

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[9] Nor would it be likely that ONJ, as Plaintiffs' experts describe it, would have gone unnoticed in such trials, if it had occurred. Etminan himself states that ONJ is a "visually appreciable" condition. Report of Mahyar Etminan ("Etminan Report") at 19 (Ex. 9).

[10] Case-control studies and cohort studies are the two main types of scientifically valid observational epidemiological studies, and they measure and compare the frequency of exposure to a particular agent in a group with the disease under study, and in a similar control group without that disease. *See* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE at 340.

**c. There Is No Proven Mechanism Showing How Oral Bisphosphonates Could Cause ONJ.**

Hellstein admits that any pathophysiological link between bisphosphonates and the development of ONJ is unproven and hypothetical. Hellstein Dep. at 304-06. No scientific evidence demonstrates that therapeutic doses of Fosamax cause bone cells – osteocytes – to die in humans. Speculations as to potential biological mechanisms by which Fosamax could cause ONJ have not progressed beyond mere hypotheses. *See, e.g.,* Hellstein Dep. at 311 (agreeing that various proposed mechanisms "need[] to be studied," were "a hypothesis," or were "speculation"); Etminan Dep. at 265, 272-73 (stating at different times, with reference to such mechanisms, that "[i]t may be one; it may be a combination of three; there may be other factors," "plus mechanisms we are not sure of," "[w]e don't know").

**d. Other Evidence Contradicts Any Claim That Oral Bisphosphonates Cause ONJ.**

Several medical claim studies have been published, which sought to utilize medical claims data to analyze whether there is a relationship between ONJ or related conditions and use of oral bisphosphonates, and found no evidence to support an association between oral bisphosphonates and ONJ:[11]

- Zavras, *et al.*, examined medical claims data for 255,757 cancer patients between 2001 and 2004, and reviewed those records for surgical procedures to the mandible or the maxilla. The authors concluded that use of oral bisphosphonates was not associated with any increased risk of jaw surgery.[12]

[11] Medical claim studies retrospectively review medical and pharmacy records to correlate health outcomes and pharmaceutical prescriptions. *See* Report of Jane A. Cauley, Dr. PH ("Cauley Report") at 11 (Ex. 25). Such studies can also use a control group, by examining records of similar patients with or without the conditions under study.

[12] Zavras, *et al.*, *Bisphosphonates Are Associated With Increased Risk For Jaw Surgery In Medical Claims Data: Is It Osteonecrosis?*, 64 J. ORAL. MAXILLOFAC. SURG. 917 (2006) (Ex. 48).

- Pazianas, *et al.*, identified women age 45 or older who had received surgery to the mandible or maxilla and who did not have cancer. Oral bisphosphonates were not associated with jaw surgery, although there was evidence that osteoporosis itself could be.[13]

- Cartsos, *et al.*, reviewed medical claims data for 700,000 patients with either osteoporosis or cancer, and identified patients who either had inflammatory jaw conditions (including osteonecrosis), major jaw surgery due to necrotic or inflammatory jaw conditions, or jaw surgery due to malignant process. No association was found, in subjects with osteoporosis, between any of these outcomes and oral bisphosphonate use.[14]

In addition, as Hellstein admits, there are no animal studies showing that alendronate in therapeutic doses causes ONJ. Hellstein Dep. at 90. There is no animal model that can test for ONJ. Marx Aredia Dep. at 203-04; Hellstein Dep. at 194. Nor have Plaintiffs cited any *in vitro* studies showing that alendronate causes ONJ.

**4. Plaintiffs' Proposed Causation Experts.**

To undercut the prevailing scientific view, Plaintiffs seek to elicit testimony from four proposed witnesses. None of these experts prescribes Fosamax, none of these experts specializes in bone biology or metabolism, and only one is an epidemiologist:

Dr. John W. Hellstein is a clinical professor of dentistry who directs a surgical oral pathology laboratory. Hellstein purports to identify a condition that he refers to as "BON." As defined by Hellstein, BON includes a myriad of symptoms also seen in other bone conditions. *See* Hellstein Report at 10-12. Hellstein contends in his report that the clinical presentation of BON is distinct from other conditions, and he relies on case reports to make this assertion. *Id.* at 12-17. He concedes, however, that ONJ has been reported in the absence of oral

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[13] Pazianas, *et al.*, *A Review Of The Literature On Osteonecrosis Of The Jaw In Patients With Osteoporosis Treated With Oral Bisphosphonates: Prevalence, Risk Factors, And Clinical Characteristics*, 29 CLIN. THER. 1548 (2007) (Ex. 49).

[14] Cartsos, *et al.*, *Bisphosphonate Use And The Risk Of Adverse Jaw Outcomes: A Medical Claims Study Of 714,217 People*, 139 J. AM. DENT. ASS'N 23 (2008) (Ex. 50).

bisphosphonates, that ONJ can have the same symptoms as BON, and that ONJ may follow other types of mouth conditions, such as osteomyelitis. Hellstein Dep. at 86-87, 90, 130, 136-38, 142, 152. Hellstein also concedes that there is no data from controlled studies establishing a higher incidence of ONJ in Fosamax patients, that no animal study shows that therapeutic doses of bisphosphonates cause ONJ, and that there is no known, tested mechanism by which Fosamax would supposedly cause ONJ. *Id.* at 90-91, 304-06.

Dr. Robert Marx is a dentist and professor of surgery, who states that he has personally seen ONJ in patients referred to him. Report of Robert E. Marx ("Marx Report") at 9-10 (Ex. 5). Marx's testimony is based primarily on case reports, personal experience, and personal theories as to the mechanism by which Fosamax supposedly causes ONJ. *See* Marx 3/27/09 Dep. at 133-34; Marx Report at 4-5; *id.* at 12, ¶ 48 (opining that his views were based on "my own experience" and a selective "review of scientific and medical literature"). As explained below, Marx' personal theories have not been subjected to any formal testing and are not supported by scientific evidence.

Dr. Mahyar Etminan is the only epidemiologist that Plaintiffs have designated for general causation issues. Etminan is, in fact, only a part-time epidemiologist, and a part-time pharmacist, from Vancouver, British Columbia. Etminan Dep. at 21-22, 35-36.[15] In his earlier writings, Etminan emphasized the need for controlled epidemiological evidence to support opinions on causation. *See* Etminan, *Evidence-Based Pharmacotherapy: Review of Basic*

[15] Etminan earned his doctoral degree in pharmacy via correspondence from Idaho State University in 2001 after he was asked to leave the degree program at the University of British Columbia. Etminan Dep. at 16-17. Approximately six years ago, he earned a masters degree in clinical epidemiology from the University of Toronto. Curriculum Vitae of Mahyar Etminan ("Etminan C.V.") (Ex. 10). One to two days a week, Etminan fills prescriptions at a pharmacy outside of Vancouver. Etminan Dep. at 36. He also works as a research scientist for the Vancouver Coastal Health Research Institute. Etminan C.V. He became an assistant professor of medicine at the University of British

*Concepts and Applications in Clinical Practice*, 32 THE ANNALS OF PHARMACOTHERAPY 1193-94 (Nov. 1998) (Ex. 46). Now, for his litigation opinion, Etminan concludes that Fosamax causes ONJ without any controlled evidence. His view is based on case reports, prevalence studies, animal data that he is not qualified to interpret, and speculation as to biologic mechanisms outside of his area of expertise. *See* Etminan Report at 9-20.

Dr. Alastair Goss is an Australian oral surgeon. In his report, Goss primarily repeats the results of a postal survey that he conducted in Australia and bases his assertion that Fosamax causes ONJ on an alleged "careful review of the international scientific literature," which he does not describe. Report of Alastair N. Goss ("Goss Report") at 5, ¶ 12 (Ex. 11).

### C. Argument In Support of Merck's Motion To Exclude General Causation Experts.

As discussed more fully in Section I, *supra*, expert opinion testimony is not admissible unless the testimony is based on sound, reliable science, and the supporting evidence and opinions drawn therefrom fit the facts of the case. *See Rezulin I*, 309 F. Supp. 2d at 539 (citing *Daubert*, 509 U.S. at 592-93); Fed. R. Evid. 702 (providing that the testimony must be based upon sufficient facts or data and the product of reliable principles and methods). The Court may consider any appropriate factors, including whether the theory has been generally accepted or has been tested, in making this determination, and the expert's opinion must be reliable *both* in total and with respect to each part. *See, e.g., Rezulin II*, 369 F. Supp. 2d at 426 (excluding opinions where "[t]he plaintiffs have no evidence for the final link in their causal chain"); *Amorgianos.*, 137 F. Supp. 2d at 174 (excluding proffered opinion that contained a speculative step). In particular, where experts seek to assemble support for novel theories from multiple, unreliable

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Columbia approximately ten months ago, but apparently receives no compensation from that institution. Etminan Dep. at 22, 29. He is not a member of any professional organizations. Etminan Dep. at 38-39.

sources, it is "within [a] District Court's discretion to conclude that the studies upon which the experts rel[y] [are] not sufficient, whether individually or in combination, to support their conclusions..." *General Electric Co. v. Joiner,* 522 U.S. 136, 146-47 (1997). That is precisely the case here. The theories of Plaintiffs' general causation experts fail because (1) they rely upon unreliable evidence, such as case reports, prevalence studies, and animal studies and (2) they rely upon mere hypotheses to explain the mechanism of how Fosamax supposedly could cause ONJ.

### 1. Plaintiffs' Experts Cannot Use Case Reports To Prove That Fosamax Causes ONJ.

As the Court concluded in *Amorgianos*, 137 F. Supp. 2d at 167, "the fundamental principles of epidemiology, which are now becoming well known to the courts" provide significant guidance as to the reliability of an expert's proposed causal hypothesis. Randomized, controlled trials provide the best evidence regarding a potential association between an exposure and a medical event, and controlled, but non-randomized, studies such as cohort and case-control studies provide the next tier of reliable evidence. *See, e.g.*, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE at 338; *Rezulin II*, 369 F. Supp. 2d at 406. As discussed previously, there is no such evidence to support Plaintiffs' contention that oral bisphosphonates cause ONJ. Instead, Plaintiffs rely exclusively on individual case reports and uncontrolled prevalence studies. Hellstein admits that such evidence cannot show that the use of an oral bisphosphonate causes a statistically significant increased risk of ONJ, because "[t]o find statistical significance, you have to have something to compare it to, which would be the relative background risk," and there is no study "that has demonstrated that oral bisphosphonates statistically significantly increased the risk for osteonecrosis of the jaw." Hellstein Dep. at 128.

**a. Case Reports And Adverse Event Reports Are Not Proper Evidence of Causation.**

Plaintiffs' experts rely extensively on individual case reports of alleged ONJ. Marx 3/27/09 Dep. at 133-34; Marx Report at 9.[16] Plaintiffs also repeatedly refer to adverse event reports ("AERs") provided to the FDA or to reports of potential ONJ provided to Merck. *See e.g.*, Marx Report at 9-10; Etminan Report at 12-13.[17] Reliance on such evidence is not a scientifically accepted methodology for establishing causation.

Uncontrolled case studies and case reports have been repeatedly rejected as the basis for causation opinions. "An uncontrolled case study or case-series report, is not actually a formal epidemiologic investigation but simply the identification of an unusual occurrence or disease." *Amorgianos*, 137 F. Supp. 2d at 167, citing ENVIRONMENTAL & OCCUPATIONAL MEDICINE 44 (William N. Rom ed., 3d ed. 1998). Case reports are not proper evidence of causation because they are mere reports of isolated events and provide no *scientific* means to measure frequency, to compare with controlled populations, or to exclude confounding factors. As the Eleventh Circuit has cautioned, case reports "reflect only reported data, not scientific methodology," and even

[16] Etminan asserts that epidemiological evidence is not needed because the FDA has ordered withdrawal of drugs from the market in certain extreme cases based on adverse event reports. Etminan Report at 4-5. This contention is a legal *non sequitur* that Plaintiffs should not be permitted to introduce at trial. Fosamax has not been removed from the market by the FDA, and the FDA requires a much lower threshold of proof before removing a drug from the market than the courts apply under the preponderance of the evidence standard in a civil case. *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 991 (8th Cir. 2001); *see also Mitchell v. Gencorp, Inc.*, 165 F.3d 778, 783 n.3 (10th Cir. 1999) (stating that government agencies use a standard of proof that is "reasonably lower than that appropriate in tort law"); *Allen v. Pennsylvania Eng'g Corp.*, 102 F.3d 194, 198 (5th Cir. 1996) (same). The FDA's power to withdraw a drug from the market has no relevance to the issues in this case.

[17] AERs are reports provided by a manufacturer to the FDA when the manufacturer receives information, from any source, whether verified or not, about adverse events reported by or about patients taking a particular prescription drug. 21 C.F.R. § 314.80(c). AERs "reflect complaints called in by product consumers without any medical controls or scientific assessment." *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1250 (11th Cir. 2005). AERs do not constitute a proper basis for testimony on causation issues because such "[u]ncontrolled anecdotal information offers one of the least reliable sources to justify opinions about both general and individual causation." *Id.*

"more detailed case reports . . . report symptoms observed in a single patient in an uncontrolled context. They may rule out other potential causes of the effect, but they do not rule out the possibility that the effect manifested in the reported patient's case is simply idiosyncratic or the result of unknown confounding factors." *Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194, 1199 (11th Cir. 2002); *McClain.*, 401 F.3d at 1254 (observing that "[s]imply stated, case reports raise questions; they do not answer them."). "The difficulty with case reports, in other words, is distinguishing between association and causation. Simply because a patient exposed to a particular substance exhibited a set of symptoms does not mean that it was the substance that caused the symptoms." *Rezulin II*, 369 F. Supp. 2d at 406.

For these reasons, courts repeatedly have excluded general causation opinions based on case reports. *See, e.g., Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 537, 539 (W.D. Pa. 2003) (concluding "that expert opinion based on [adverse event report]s and anecdotal case reports is not admissible" and stating that "[t]his Court notes that its conclusion is consistent as well with that of numerous other federal courts which have also rejected general causation opinions based on AERs and case reports") (citation omitted); *Newton v. Roche Labs., Inc.*, 243 F. Supp. 2d 672, 680 (W.D. Tex. 2002) (noting that "[t]he Fifth Circuit and many other courts have soundly rejected case reports as an acceptable basis for causation"); *Siharath v. Sandoz Pharms. Corp.*, 131 F. Supp. 2d 1347, 1361 (N.D. Ga. 2001) (stating that case reports "cannot establish general causation"), *aff'd sub nom. Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194 (11th Cir. 2002); *Glastetter v. Novartis Pharms. Corp.*, 107 F. Supp. 2d 1015, 1028 (E.D. Mo. 2000) ("At the outset, the Court notes that plaintiffs' experts' reliance on case reports is not sufficient to make their causation opinions reliable under *Daubert*."), *aff'd*, 252 F.3d 986 (8th

Cir. 2001).[18]

Marx himself illustrates the unreliability of case reports and adverse event reports. Marx claims in his report that Merck has received a number reports of ONJ allegedly related to bisphosphonates, but he has no information as to whether any of those reports are accurate, or even as to whether any of them actually involved ONJ. Marx 3/27/09 Dep. at 132-33; Marx Aredia Dep. at 864-65. Such reports are particularly unreliable where, according to Marx, "mainstream" dentists are "uncertain and confused" on the issue of ONJ, and Marx has seen patients referred to him with exposed bone who were wrongly diagnosed by other dentists as having ONJ. Marx Class Cert. Dep. at 135; Marx Aredia Dep. at 176-77. Even Marx concedes that some patients reported in the literature as having bisphosphonate associated ONJ may have had exposed bone due to agents or conditions unrelated to bisphosphonates. Marx Aredia Dep. at 618.

The unreliability of an opinion based upon case reports is demonstrated by Marx's present attempt to reverse his long-standing position that Fosamax cannot cause ONJ unless it has been taken continuously for three years. Until he filed his expert report in January 2009,

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[18] *See also Castellow v. Chevron USA*, 97 F. Supp. 2d 780, 787 (S.D. Tex. 2000) (agreeing that "attempts to form opinions regarding medical causation based on documents such as [anecdotal case reports or collections of case reports] are unscientific and speculative") (amendments in original; citation omitted)); *Hollander*, 95 F. Supp. 2d at 1235-38 (noting that "case reports have been repeatedly rejected as a scientific basis for a conclusion regarding causation"); *Nelson v. Am. Home Prods. Corp.*, 92 F. Supp. 2d 954, 969 (W.D. Mo. 2000) ("At most, these case reports relay a basis for scientific hypotheses; they do not demonstrate a causal link sufficient for admission to a finder of fact in court"); *Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1411 (D. Or. 1996) ("[C]ase reports and case studies are universally regarded as an insufficient scientific basis for a conclusion regarding causation because case reports lack controls. . . . Therefore, these cannot be the basis of an opinion based on scientific knowledge under *Daubert*") (citations omitted); *Jones v. United States*, 933 F. Supp. 894, 898 (N.D. Cal. 1996) (stating that anecdotal case reports are not derived through the scientific method and "falls far short of the proven, cause-and-effect relationship that is necessary to satisfy the *Daubert* standard"), *aff'd*, 127 F.3d 1154 (9th Cir. 1997); *see also Rezulin II*, 369 F. Supp. 2d at 411 n.92 (noting that "[t]he case reports that the plaintiffs and their experts say are examples or illustrations of an injury silently caused or exacerbated by Rezulin do not support their assertions").

Marx had been emphatic that, based upon his "analysis," Fosamax and other oral bisphosphonates ***required*** three years of continuous use before sufficient bisphosphonate could accumulate in the jaw to create a risk:

- Marx agreed at his deposition on class issues that he "see[s] no risk to users of less than three years." Marx Class Cert. Dep. at 221.

- Marx has stated in peer-reviewed scientific articles that "3 years or 156 continuous weekly doses...are ***required*** to place patients who take Fosamax or Actonel into the risk range." Sawatari, *et al.*, *Bisphosphonates and bisphosphonate induced osteonecrosis*, 19 ORAL MAXILLOFACIAL SURG. CLIN. N. AM. 487-498 (2007), at 490 (co-authored by Marx, emphasis added) (Ex. 51); *see also* Marx, Guest Editorial, 28 INT'L J. PERIODONTAL RESTORATIVE DENTISTRY 5-6 (2008), at 5 (stating that "oral BIONJ risk ... does not begin until after about 3 years of oral BP use") (Ex. 52).

- In testimony about Fosamax that he gave in the Aredia and Zometa litigation, Marx testified that "[o]ur studies have ***indicated clearly*** that it takes three years of exposure with Fosamax. . . to put a person at risk." Marx Aredia Dep. at 48 (emphasis added).

- Marx took the same position in his recent book, where he concluded that "regular use of an oral bisphosphonate for a period of less than 3 years suggests minimal or no risk." Marx, ORAL & INTRAVENOUS BISPHOSPHONATE-INDUCED OSTEONECROSIS OF THE JAWS 82, 87 (Quintessence Publ., 2007) (Ex. 53).

Marx now attempts a 180 degree reversal of this view—thereby highlighting his unscientific reliance on case reports and his willingness to twist his opinions on the biologic mechanism for litigation purposes. Marx now asserts that he can no longer determine the usage of Fosamax at which an increased risk for ONJ supposedly occurs. *See* Marx 3/27/09 Dep. at 205. Marx does not base this diametrically different opinion on a new study, new data, or new theory regarding mechanism, but instead claims only that, at some time in 2008, he reviewed his database and found five patients who, according to Marx's records, had either taken Fosamax for less than three years or who may not have taken Fosamax continuously. *Id.* at 204-07. These were not new patients–they had always been in his database and he believes his previous characterizations of them were incorrect. *Id.* Marx could not testify as to how many of these

five took Fosamax for less than three years and how many took Fosamax non-continuously for more than three years. *Id.* at 207. Based on these unspecified five cases, Marx has reversed course, repudiated a view that he has repeatedly and forcefully stated in the scientific community, and testified that his prior 2007 peer-reviewed article was inaccurate because he was mistaken about his patients' use of Fosamax. *Id.* at 208. Case reports are not reliable—Marx published and testified based on case reports that there was no risk at less than three years' use, then turned around on a dime because, he said, he had misinterpreted five of those case reports. It is abundantly clear why courts do not accept case reports as the basis for a scientific causation opinion.

**b. Prevalence And Animal Studies Do Not Make These Opinions Reliable And Must Be Viewed With Caution.**

Plaintiffs' experts also supplement their opinions with citations to prevalence and animal studies, none of which can prove that Fosamax causes ONJ. Surveys that measure the prevalence of a disease are not significantly different from case reports. In *Amorgianos*, the Court concluded that prevalence studies "usually represent preliminary or pilot investigations used to screen for possible workplace hazards or to generate hypothesis for testing in more complex designs." 137 F. Supp. 2d at 168 (citation omitted). The Court explicitly contrasted such uncontrolled studies with epidemiologically valid, controlled studies such as "cohort studies, which test for the incidence of a health condition in a randomly selected group of exposed workers and a randomly selected group of unexposed workers over time," and case-control studies, "which compare the exposure histories of a group of workers who exhibit a particular health condition with a group of workers who do not exhibit the health condition but who are comparable in characteristics other than exposure." *Id.* (citations omitted). Concluding that controlled studies are "the most informative investigations used to test specific etiological

hypotheses and to confirm and quantify degrees of health risk related to causal exposures," the Court found it significant that "none of the epidemiological studies cited by plaintiffs' experts was a cohort or case-control study." *Id.* (citations omitted).

The prevalence studies that Plaintiffs cite cannot show that oral bisphosphonates cause ONJ because they contain serious methodological problems and they make no effort to determine the rate of occurrence of ONJ in non-bisphosphonate users or to determine whether oral bisphosphonates *increased* the risk of ONJ (as compared to similarly situated patients who did not take oral bisphosphonates).[19] Goss himself conceded in a consensus paper that his survey was merely "a retrospective postal survey with no validated or adjudicated diagnosis," that "from an epidemiological view, ***should be viewed with caution***." Sambrook, *et al.*, *Bisphosphonates And Osteonecrosis Of The Jaw*, 35 AUST. FAM. PHYSICIAN 801, 802 (2006) (co-authored by Goss, emphasis added) (Ex. 57); *see also* Deposition of Alastair N. Goss of 03/27/09 ("Goss Dep.") at 169-70 (Ex. 12). As Etminan admitted, these surveys only show that "ONJ happens in a cohort of bisphosphonate users." Etminan Dep. at 195. None of the surveys determined whether there is a statistically significant association between ONJ and alendronate, and none of them conclude that oral bisphosphonates increase the risk of ONJ beyond the risks incurred by similarly situated patients not taking oral bisphosphonates.[20] *See Joiner*, 522 U.S. at 145

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[19] Plaintiffs cite (1) an Australian postal survey conducted by Goss, among others and published under lead author Mavrokokki, Mavrokokki, T., *et al.*, *Nature And Frequency Of Bisphosphonate-Associated Osteonecrosis Of The Jaws In Australia*, 65 J. Oral Maxillofac Surg 415 (2007) ("Mavrokokki") (Ex. 54); (2) a study based on a review of records of "active patients" at the University of Southern California School of Dentistry ("the USC Survey"), Sedghizadeh, P., *et al.*, *Oral Bisphosphonate Use And The Prevalence Of Osteonecrosis Of The Jaw*, 140 J. AM. DENT. ASS'N 61 (Jan. 2009) (Ex. 55); and (3) an unpublished survey of members of Kaiser Permanente of Northern California of which only the abstract and results are available for review ("the PROBE study"), Lo, J., *et al.*, *The Kaiser Permanente PROBE Study*, 10 KAISER PERM. NORTHERN CAL. QUARTERLY NEWSLETTER: RESEARCH UPDATE 1, 16 (2008) (Ex. 56)

[20] The Mavrokokki study expressly noted that it found no statistically significant associations, except that there seemed to be weak evidence that patients taking alendronate had less severe cases of

(emphasizing that plaintiffs' experts were relying upon studies that did not themselves draw the conclusions that the experts wanted to assert); Hellstein Dep. at 83 (admitting that the USC study did not "state anywhere that oral bisphosphonates increased the risk for osteonecrosis of the jaw over what would otherwise be experienced in similarly situated osteoporotic patients," because "[t]hat was not what their purpose was"); Etminan Dep. at 289-90 (admitting that he has no empirical evidence of an association between Fosamax and ONJ "[b]ecause we don't have a baseline risk in the population").[21] Goss's concession that such prevalence studies "should be viewed with caution" itself lays to rest any question whether such surveys are reliable. They are not; and are essentially nothing more than a collection of case reports.

The reliability of these experts' opinions is further undercut by their emphasis on only a few of the applicable studies, while ignoring those with which Plaintiffs disagree. *See supra*, § II.B.3.d.[22] "[I]f the relevant scientific literature contains evidence tending to refute the expert's theory and the expert does not acknowledge or account for that evidence, the expert's opinion is

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ONJ. Mavrokkokki, *supra*, at 418 (Ex. 54). The study observed that "[t]his retrospective postal survey with multiple assumptions and without independent assessment of cases, shows the need for prospective clinical trials." *Id.* at 417, 422.

[21] The PROBE study in particular cannot be a sound basis for a causation opinion in this case, where Plaintiffs' experts formed their opinions well before the study was performed and now purport to rely only on the study's abstract. As the Court articulated in *Amorgianos*, abstracts are "a place where research starts, not where it ends," because "[t]he synopsis of a medical article given in its abstract will, of necessity, fail to include details regarding the methodology and conclusions of the summarized study that may attenuate or even destroy its relevance to the issue in question." *Amorgianos*, 137 F. Supp. 2d at 189.

[22] *See also* Hoff, *et al.*, *Frequency And Risk Factors Associated With Osteonecrosis If The Jaw In Cancer Patients Treated With Intravenous Bisphosphonates*, 23 J. BONE MINER. RES. 826 (2008) (finding that both dental extraction and a history of osteoporosis was associated with increased risk of ONJ, even after controlling for bisphosphonate use) (Ex 58); Walter, *et al.*, *Prevalence Of Bisphosphonate Associated Osteonecrosis Of The Jaw Within The Field Of Osteonecrosis*, 15 SUPPORT CARE CANCER 19 (2007) (finding no increased prevalence of oral bisphosphonate use among patients with osteonecrosis, sequestered bone, or bone infection in a hospital clinic of oral and maxillofacial patients in Germany) (Ex. 59); Murad, *et al.*, *Bisphosphonates And Osteonecrosis Of The Jaw: A Retrospective Study*, 13 ENDOCR. PRACT. 232 (2007) (finding no evidence of increased frequency of ONJ in oral bisphosphonate

unreliable." *Rezulin II*, 369 F. Supp. 2d at 425. Plaintiffs' experts cannot "selectively [choose] [their] support from the scientific landscape." *Carnegie Mellon Univ. v. Hoffman-La Roche, Inc.*, 55 F. Supp. 2d 1024, 1039 (N.D. Cal. 1999) (citation omitted); *Miller v. Pfizer, Inc.*, 196 F. Supp. 2d 1062, 1086-87 (D. Kan. 2002) (noting that "selective reliance . . . 'is not generally accepted practice'") (citation omitted).

Nor can Plaintiffs' experts rely on animal testing. *See* Etminan Report at 14-15. As Hellstein concedes, there is no animal model in which therapeutic doses of Fosamax have been demonstrated to produce ONJ. Hellstein Dep. at 91 (admitting that he was not "aware of any animal model in which it has been demonstrated that therapeutic does of alendronate cause or contributed to osteonecrosis of the jaw"); Hellstein Dep. at 194 (stating, when asked if he was "aware of any studies in an animal model or in humans that indicate that therapeutic doses of alendronate caused an abnormal level of bone remodeling in the jaw of patients who have osteonecrosis of the jaw," that "I know of no study, and I don't know that it could be done."). Extrapolations of animal studies to human beings are not reliable "in the absence of a scientific explanation of why such extrapolation is warranted." *Hall*, 947 F. Supp. at 1410; *Rezulin II*, 369 F. Supp. 2d at 407 (noting that "different species have important physiological differences" and "the high doses often used in animal studies may not correspond to considerably lower concentrations of a drug or other substance to which humans are in reality exposed."). Plaintiffs have made no such showing here.[23] All animal studies conducted with Fosamax, including those

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patients, in retrospective chart review utilizing CPT codes suggestive of ONJ and bisphosphonate use) (Ex. 60).

[23] Etminan cites no research or rationale to justify his reliance on a 1981 study in which rice rats were fed large amounts of clodronate and a high-sucrose diet and developed exposed bone in their mouths Etminan Report at 14-15 (citing Gotcher & Jee, *The Progress Of The Periodontal Syndrome In The Rice Rat; II. The Effects Of A Disphosphonate On The Periodontium*, 16 J. PERIODONTAL RES. 441 (1981) (Ex. 61)). Rice rats are a genetically unique strain of rat that experiences severe and aggressive periodontal disease unlike that experienced by humans; their diet was specifically intended to induce the

in animal models with periodontal disease, have consistently failed to show any evidence of exposed bone, and no animal study using therapeutic doses of Fosamax has produced exposed, non-healing bone in the jaw.[24]

### 2. Plaintiffs' Experts Cannot Rely Upon Speculative Mechanisms By Which Fosamax Would Allegedly Cause ONJ.

Plaintiffs' experts cannot overcome their lack of valid epidemiological evidence by speculating as to various unproved mechanisms by which ONJ may or may not be caused by Fosamax. *See Moberly ex rel. Moberly v. Secretary of Health and Human Services*, 85 Fed. Cl. 571 (2009) (excluding testimony as to theory by which vaccine could allegedly cause neurological damage, where theory had never been tested). As an initial matter, it is not appropriate to discuss "mechanisms" where no association has been proven. *See, e.g., Gannon v. United States*, 571 F. Supp. 2d 615, 624 (E.D. Pa. 2007) (excluding expert testimony on general causation and stating that "epidemiological and biological evidence are key components to all well-recognized scientific frameworks that examine causation of human diseases" and that "[i]f either epidemiological or biological evidence fails to support a causal connection or is otherwise inconclusive, one cannot conclude with any degree of certainty that a pathogen such as a virus is the cause of a disease such as human cancer"). Because Plaintiffs have failed to provide epidemiological evidence of a statistically significant association between Fosamax and ONJ, their contentions as to mechanism are not relevant. Equally important, the mechanisms cited by

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aggressive effects of periodontal disease, and Clodronate and Fosamax are different compounds with different mechanisms of action. This study is not relevant here. *See Joiner*, 522 U.S. at 144-45 (rejecting plaintiff's attempt to rely upon studies showing alevelogenic carcinomas in rats where the plaintiff claimed to have suffered from small cell carcinoma, an entirely different disease).

[24] Reddy, *et al.*, *Alendronate Treatment Of Naturally-Occurring Periodontitis In Beagle Dogs*, 66 J. PERIODONTOL. 211 (March 1995) (Ex. 62); Brunsvold, *et al.*, *Effects Of A Bisphosphonate On Experimental Periodontitis In Monkeys*, 63 J. PERIODONTOL. 825 (1992) (Ex. 63).

Plaintiffs' experts, when subjected to peer review, have been recognized as unproven hypotheses.

Plaintiffs' experts concede that a mechanism has not been demonstrated. As Etminan testified, "[i]t may be one; it may be a combination of three; there may be other factors" or even other "mechanisms we are not sure of," "[w]e don't know." Etminan Dep. at 265, 272-73. Hellstein and Etminan, in fact, admit that their theories are speculative. Hellstein admitted at his deposition that any pathophysiological link between bisphosphonates and the development of ONJ is unknown and unproven. Hellstein Dep. at 304-06.[25] Etminan, who has no relevant qualifications to discuss this topic, made the same admission in a published, peer-reviewed article in June 2008. *See* Etminan, *Use of Oral Bisphosphonates and the Risk of Aseptic Osteonecrosis: A Nested Case-Control Study*, 35 J. RHEUMATOLOGY 691-698 (2008) (Ex. 64); Etminan Dep. at 267-69.[26] Where even Plaintiffs' designated experts cannot agree on a single mechanism, and concede that no such mechanism has been proven, they cannot properly speculate to the jury as to their hypotheses.

[25] While Hellstein speculated that Fosamax abnormally decreases the level of bone remodeling, he admitted that no studies in humans or animals have indicated that therapeutic doses of Fosamax cause an abnormal level of bone remodeling. Hellstein Dep. at 194. Hellstein also admitted that his other contention that oral bisphosphonates may inhibit the body's ability to resolve bacteria in the mouth also was unproven. *Id.* at 306-08 (stating that "there is an implication that is out there" but "[t]he study . . . needs to be done"). Hellstein's speculations as to biological mechanism are no more than a "hypothesis," by his own admissions. Hellstein Dep. at 311

[26] Etminan admits that he is not a bone scientist, not a vascular scientist, "or a basic pharmacologist," and has "no special training or expertise in regard to oversuppression or vascular insult." Etminan Dep. at 266. He could not "give you the step-by-step" of any of the mechanisms he purported to cite, and he could not state with scientific certainty that any of those mechanisms were correct. *Id.* at 266-68.

### 3. The Reliability Of The Proffered General Causation Testimony Is Undermined By Many Additional Factors.

#### a. Plaintiffs' Experts Cannot Separate ONJ Allegedly Caused By Oral Bisphosphonates From Other Mouth Conditions.

The reliability of the case reports, prevalence studies, and other information cited by Plaintiffs' experts is significantly undermined by the fact that ONJ occurs in the absence of oral bisphosphonates, and there is no reliable method to distinguish between ONJ that is allegedly caused by an oral bisphosphonate and ONJ that originates from some other source. *See, e.g., Pick v. Am. Med. Sys., Inc.*, 958 F. Supp. 1151, 1178-79 (E.D. La. 1997) (rejecting proffered scientific testimony regarding "Systemic Coccal Disease," where that condition could not be reliably distinguished from other conditions with similar symptoms); *Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 885 (10th Cir. 2005) (noting that observations alone, in the absence of "supporting epidemiological evidence," "cannot define a disease").

Plaintiffs' experts, and particularly Hellstein, use a variable and non-specific definition of ONJ that includes symptoms, such as exposed bone, that may be caused by many mouth conditions. None of these experts cite any published or peer reviewed research that shows any pathological or measurable difference between ONJ that occurs when a patient is taking a bisphosphonate and exposed bone or delayed healing in the mouth in other circumstances. Even though Hellstein spends a significant portion of his report arguing that "BON" was an identifiable condition that could be separated from other causes of ONJ, Hellstein admitted at his deposition that there is not a distinct pathologic or histomorphologic feature of an ONJ specimen in a patient who took a bisphosphonate that would permit him to conduct an inspection and determine that a patient with osteonecrotic bone had been taking a bisphosphonate. Hellstein Dep. at 103-05. Hellstein believes that there are "clues" that might "lead me to further question

what is going on," but he has never systematically analyzed his clues, has never published on the topic, and has never subjected his view to peer review. *Id.* at 106-07 (also stating that he has never conducted any study in a blind fashion to identify "from a scientifically sound standpoint features that are consistent with BON as opposed to other causes of osteonecrosis of the jaw").[27] Plaintiffs can point to no scientifically valid study showing that ONJ presents in a different form in patients taking an oral bisphosphonate than in patients who have exposed bone in their jaws resulting from other conditions. Consequently, it is not possible for Plaintiffs to reliably contend either that any individual case report is related to oral bisphosphonate use or that any individual Plaintiff's alleged injury is related to oral bisphosphonate.

**b. The Bradford Hill Criteria Cannot Be Reliably Applied, Etminan Is Not Qualified To Apply Them, And They Do Not Support Etminan's Conclusions.**

Etminan seeks to bolster his opinion by misapplying the "Bradford Hill" criteria. As described in *Modern Epidemiology*, which Etminan describes as the "holy grail of epidemiology textbooks,"[28] Sir Austin Bradford Hill set out in 1965 a list of "considerations or 'viewpoints'" that might be used as "considerations in attempting to distinguish causal from non-causal associations that were already 'perfectly clear-cut and beyond what we would care to attribute to the play of chance.'" Rothman, K., et al., MODERN EPIDEMIOLOGY (3rd ed., Wolters Kluwer 2008), at 26 (Ex. 65). The Bradford Hill criteria were developed as a tool for epidemiologists to apply ***after*** an association has been proven with valid epidemiological evidence. *Dunn v. Sandoz Pharms. Corp.*, 275 F. Supp. 2d 672, 678 (M.D.N.C. 2003) (excluding proposed expert

[27] [redacted]

[28] Etminan Dep. at 102.